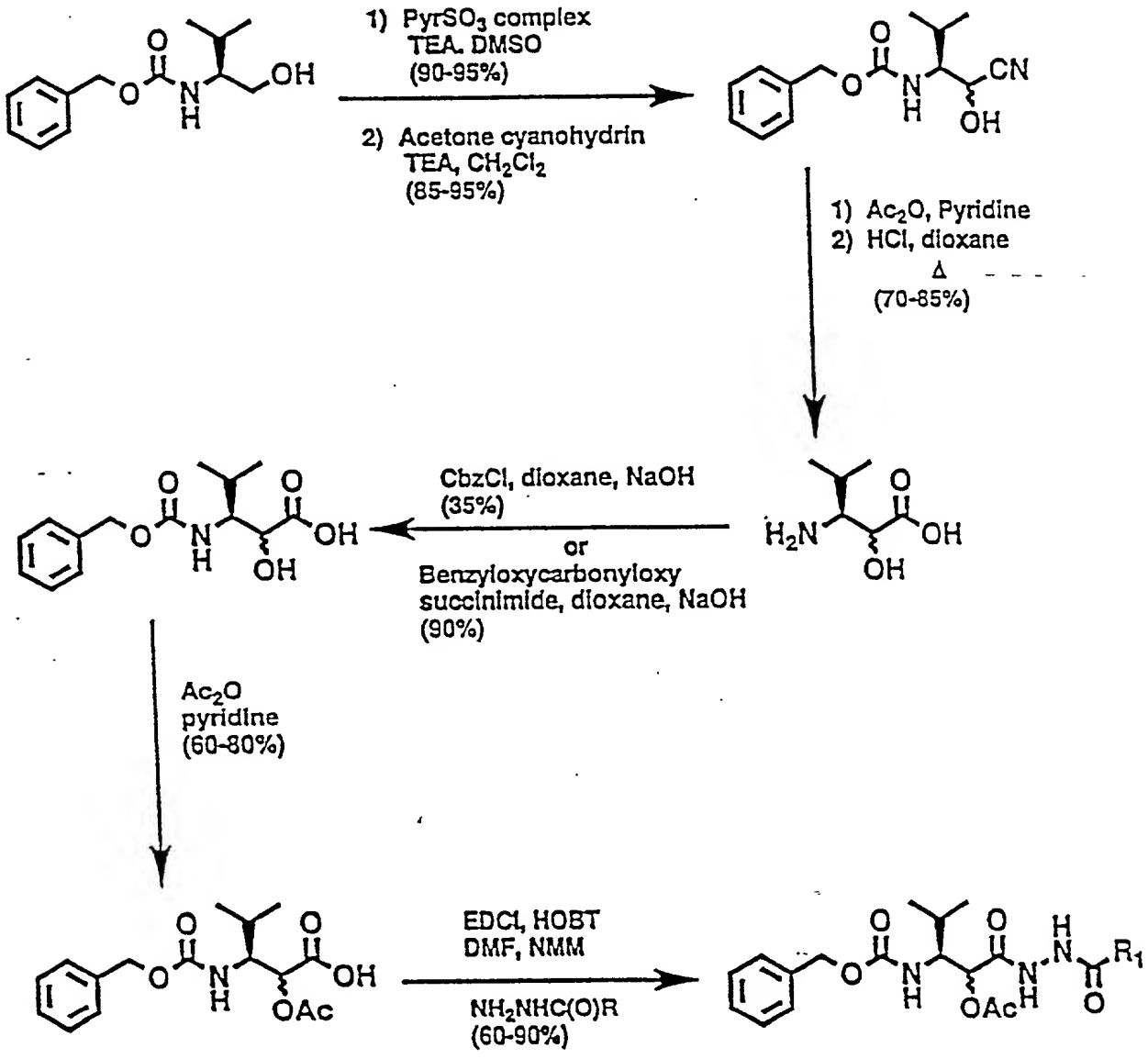
Figure 1

General Synthetic Scheme for 1,3,4-Oxadiazole Inhibitors



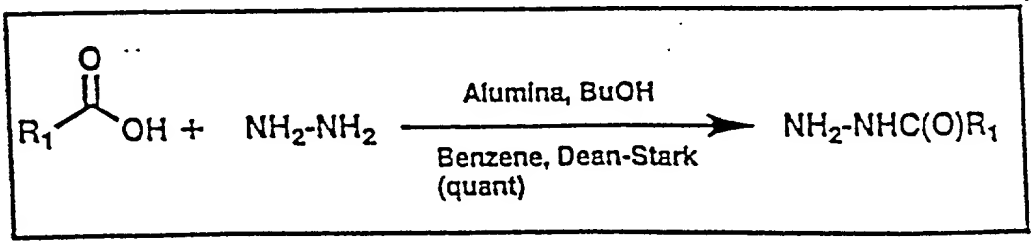


Figure 2

General Scheme for 1,3,4-Oxadiazole Inhibitors - Continued

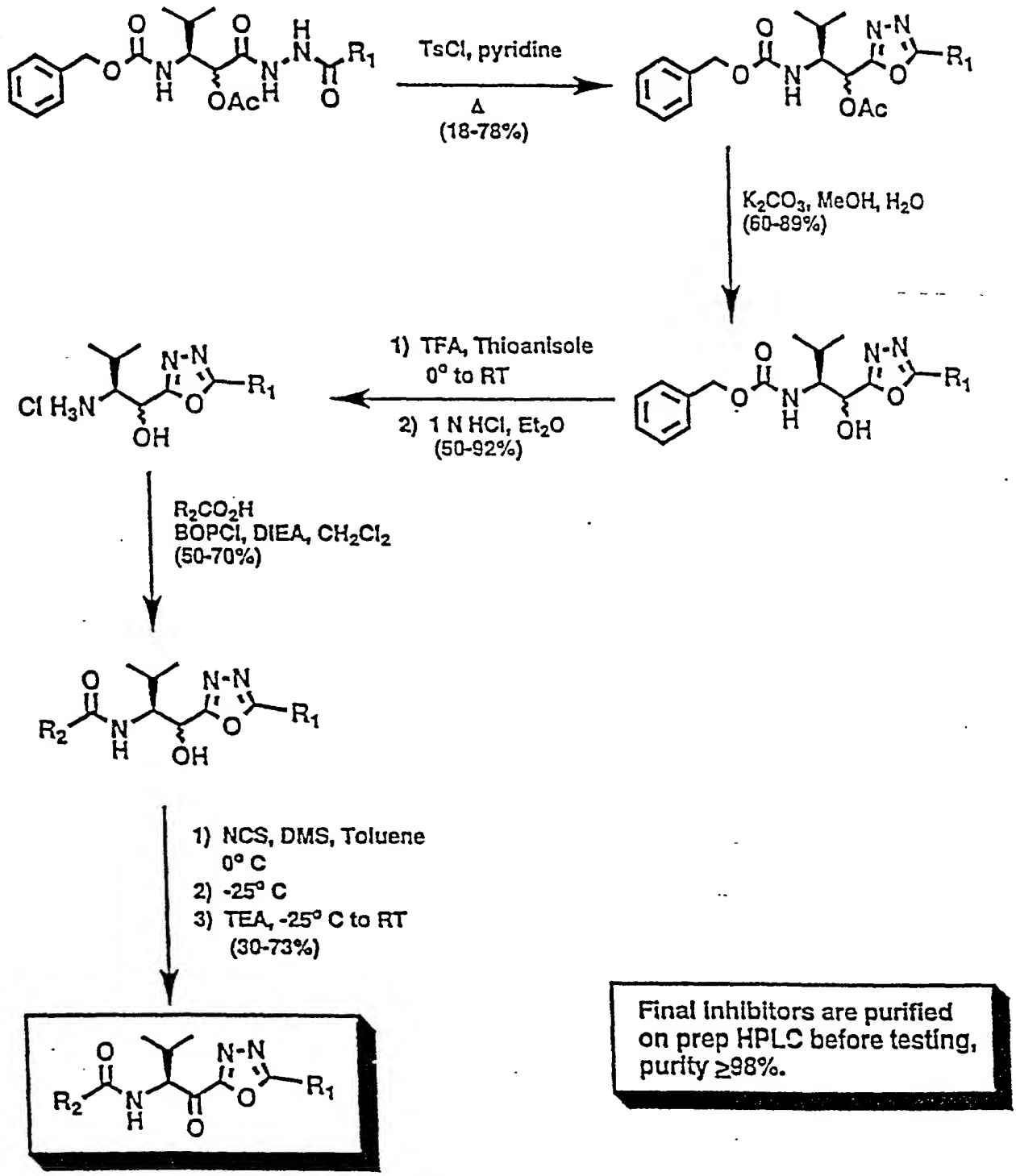


Figure 3

General Synthetic Scheme for 1,2,4-Oxadiazole Inhibitors

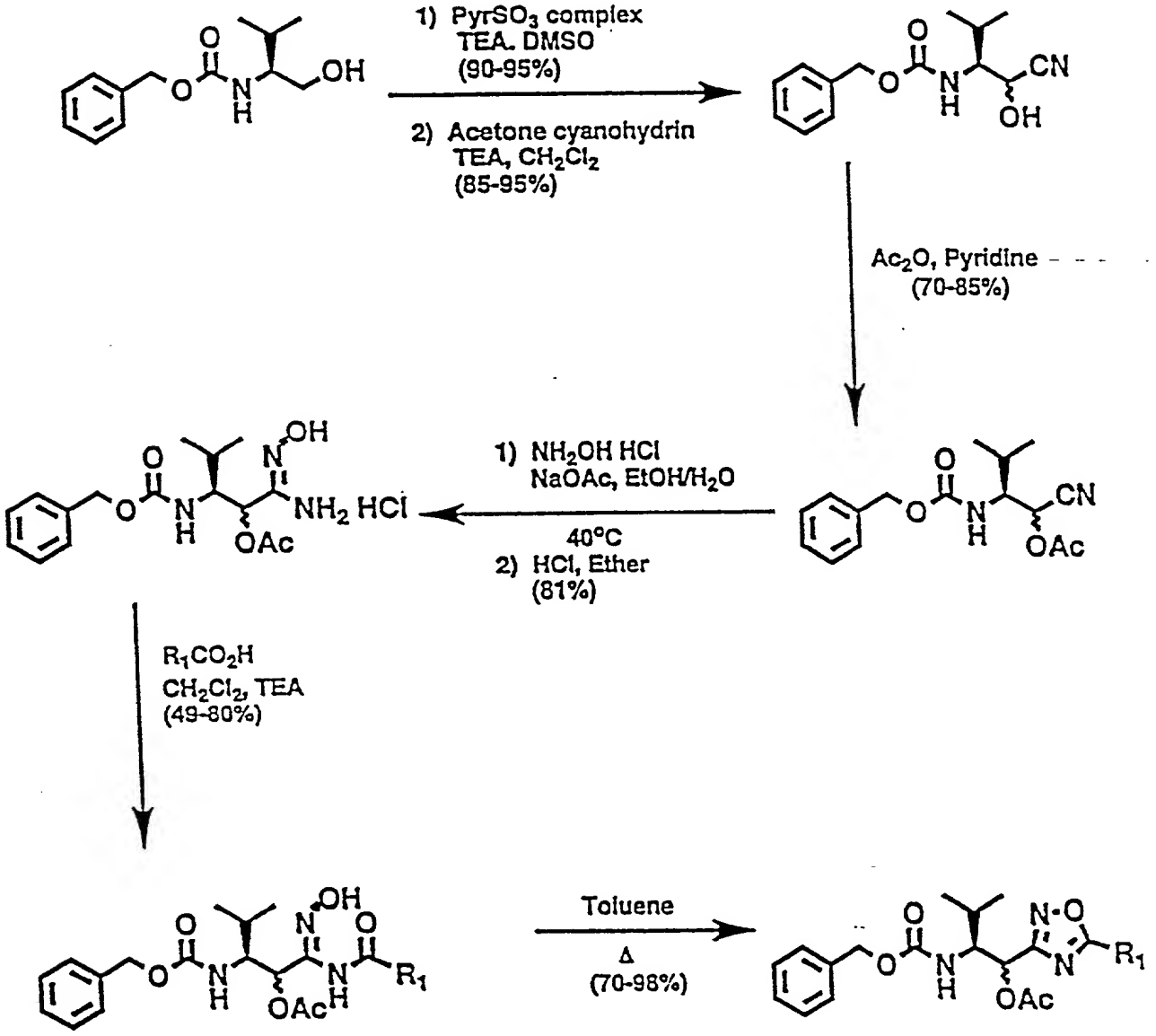


Figure 4

General Synthetic Scheme for 1,2,4-Oxadiazole inhibitors (Continued)

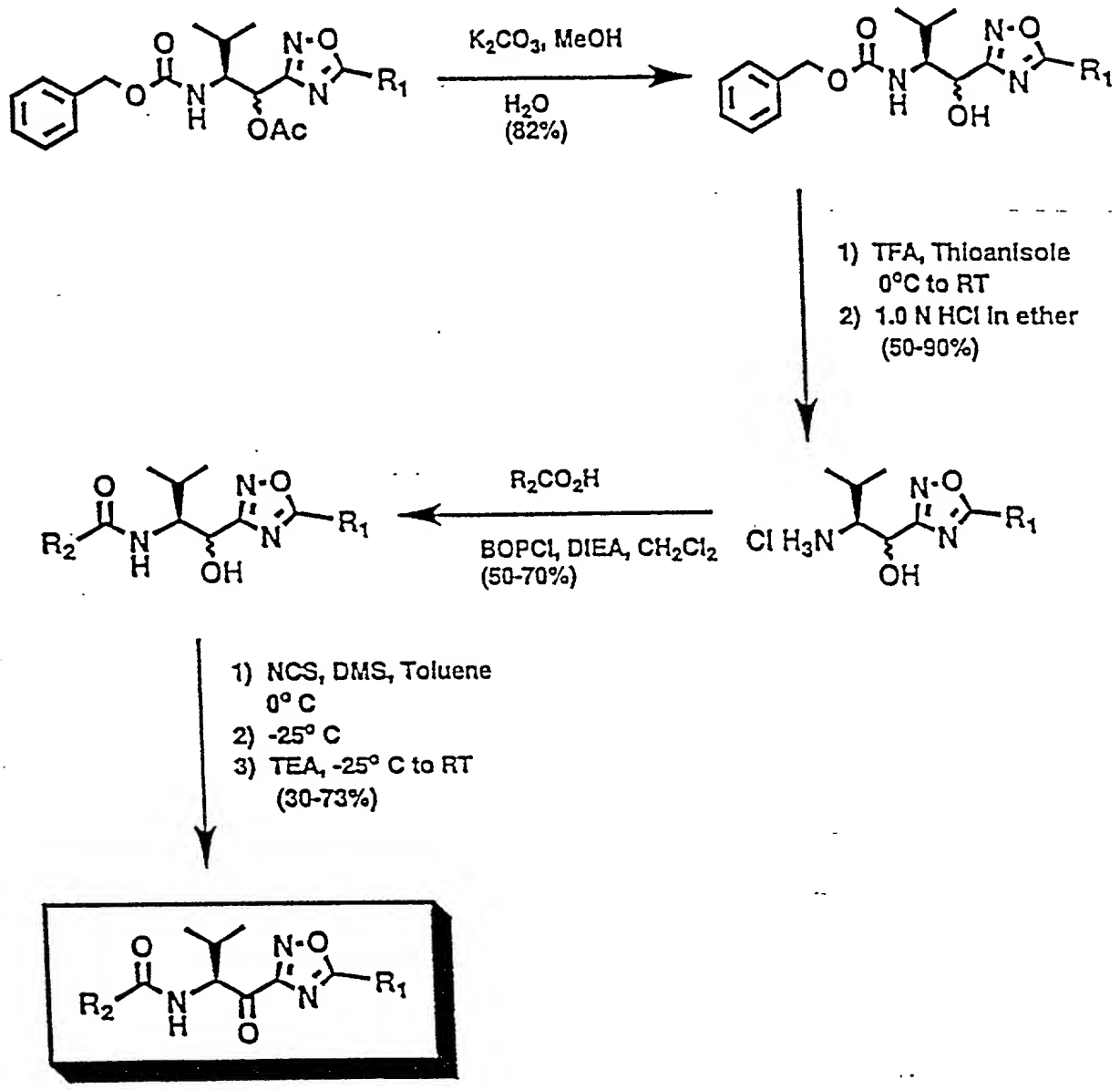


Figure 5

General Synthetic Scheme for P_2-P_3 Modified Based Inhibitors

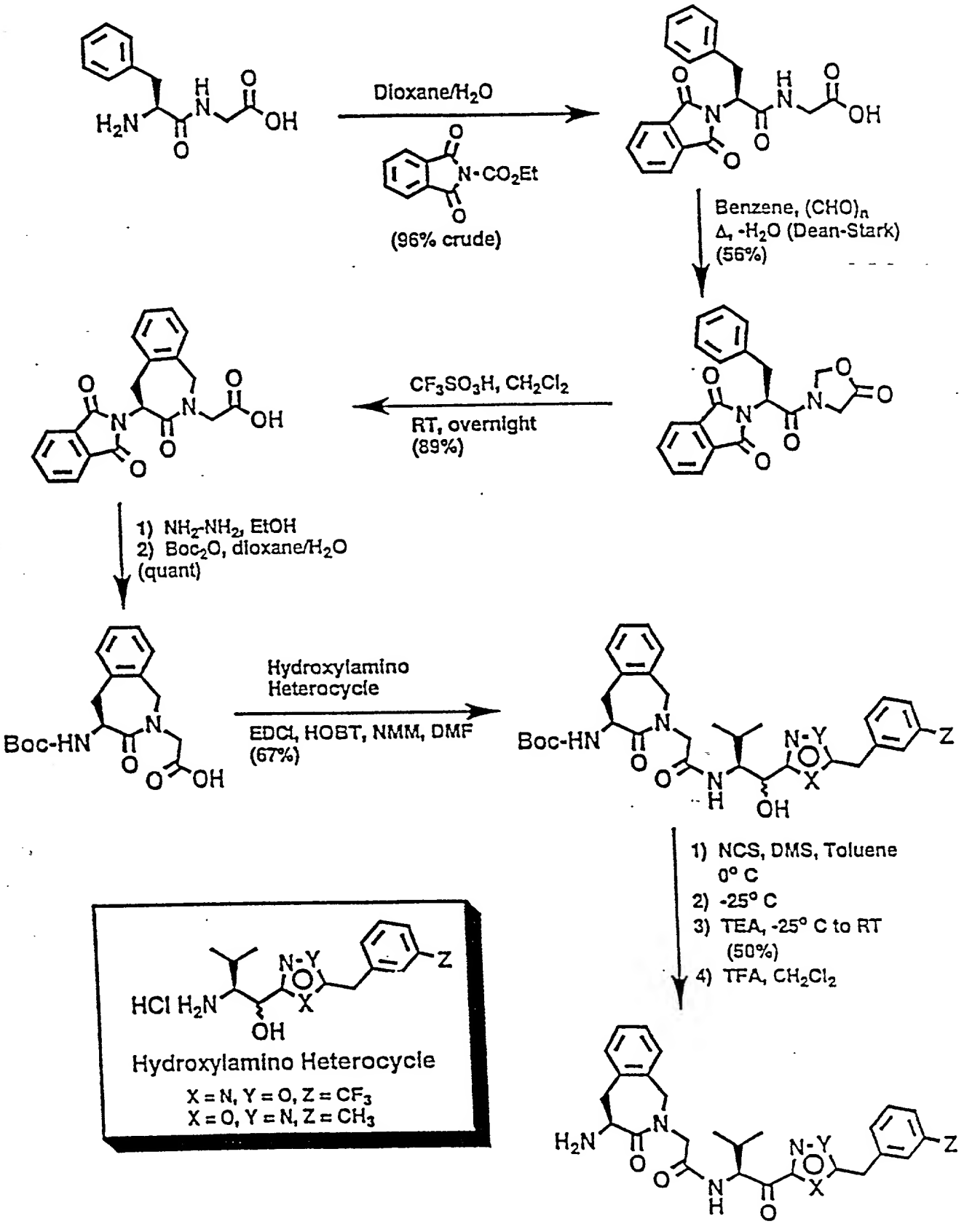


Figure 6

Synthetic Scheme for P_2-P_3 Modified Inhibitors

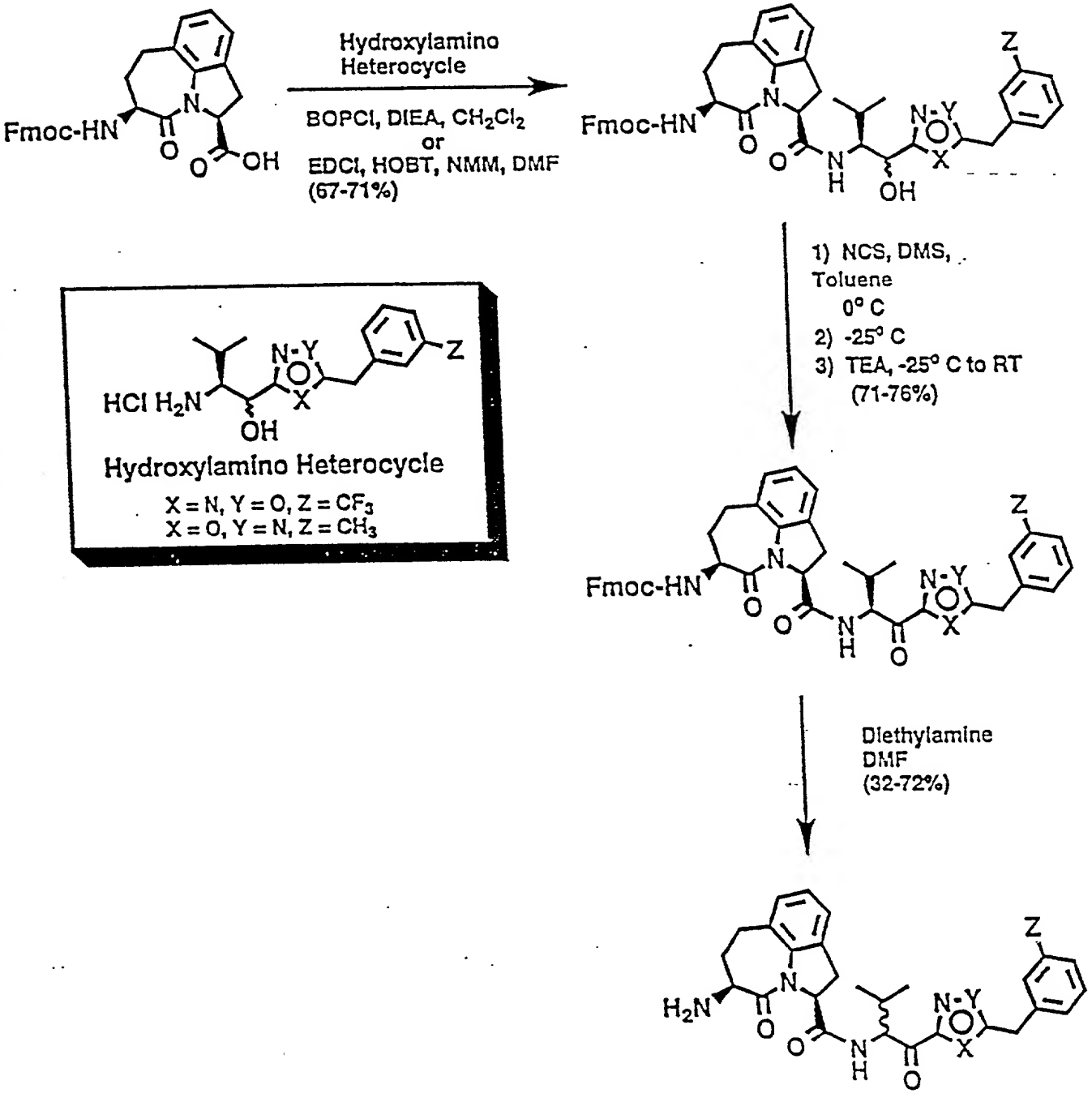


Figure 7

Synthetic Scheme for P_2-P_3 Modified Inhibitors

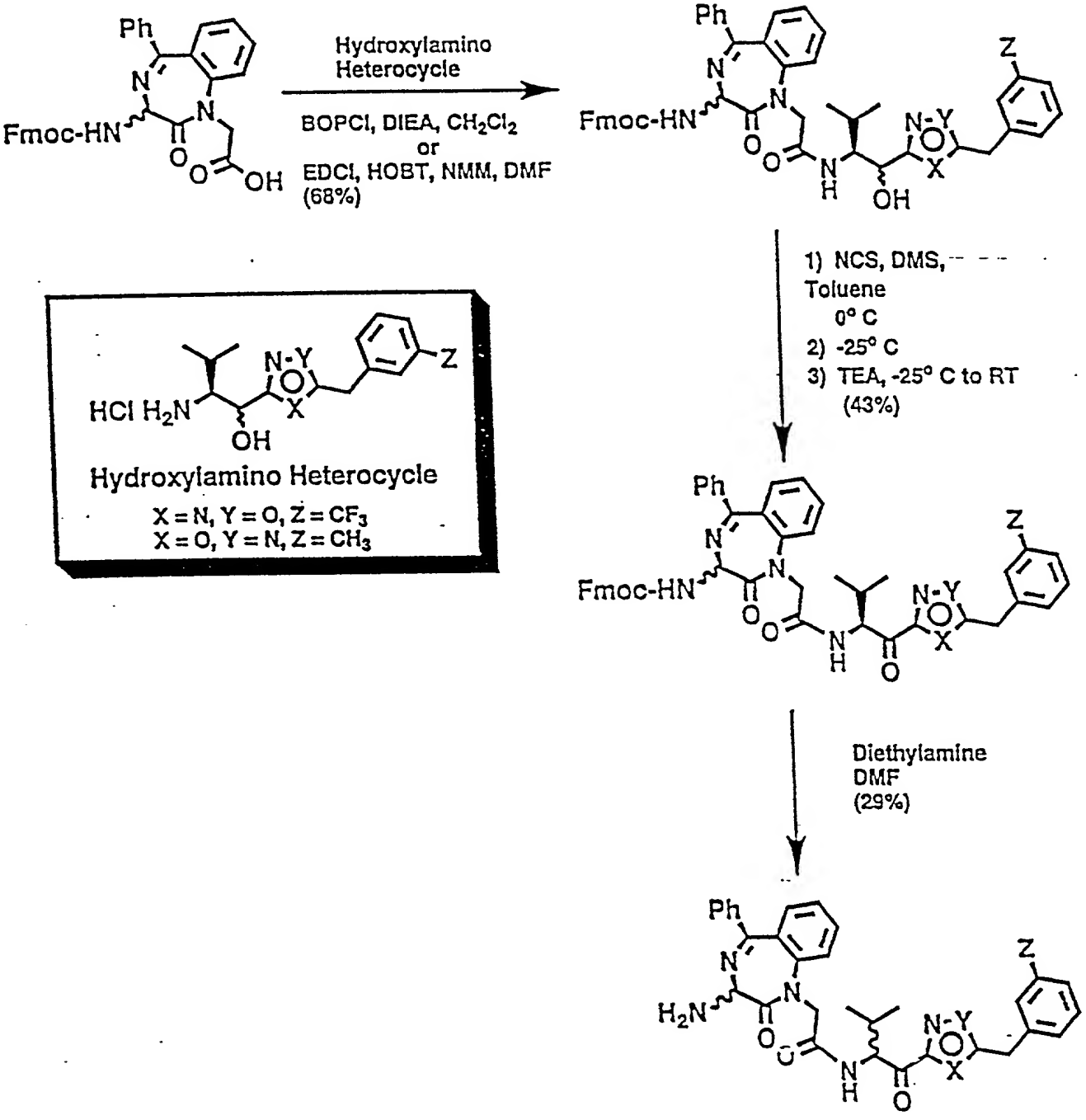


Figure 8

General Synthetic Scheme for P_2-P_3 Modified Inhibitors

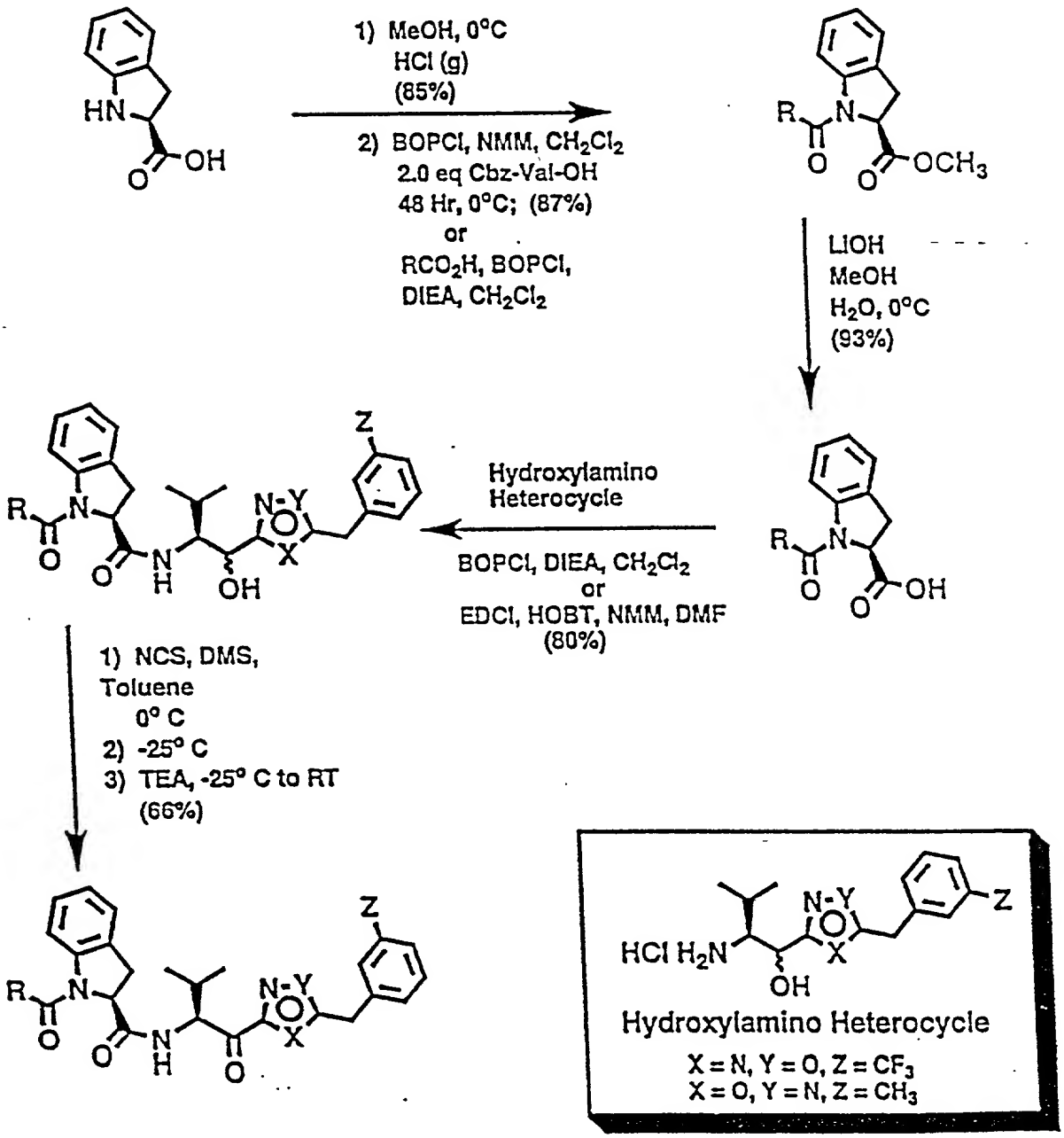


Figure 9

Synthetic Scheme for P_2-P_3 Modified Inhibitors

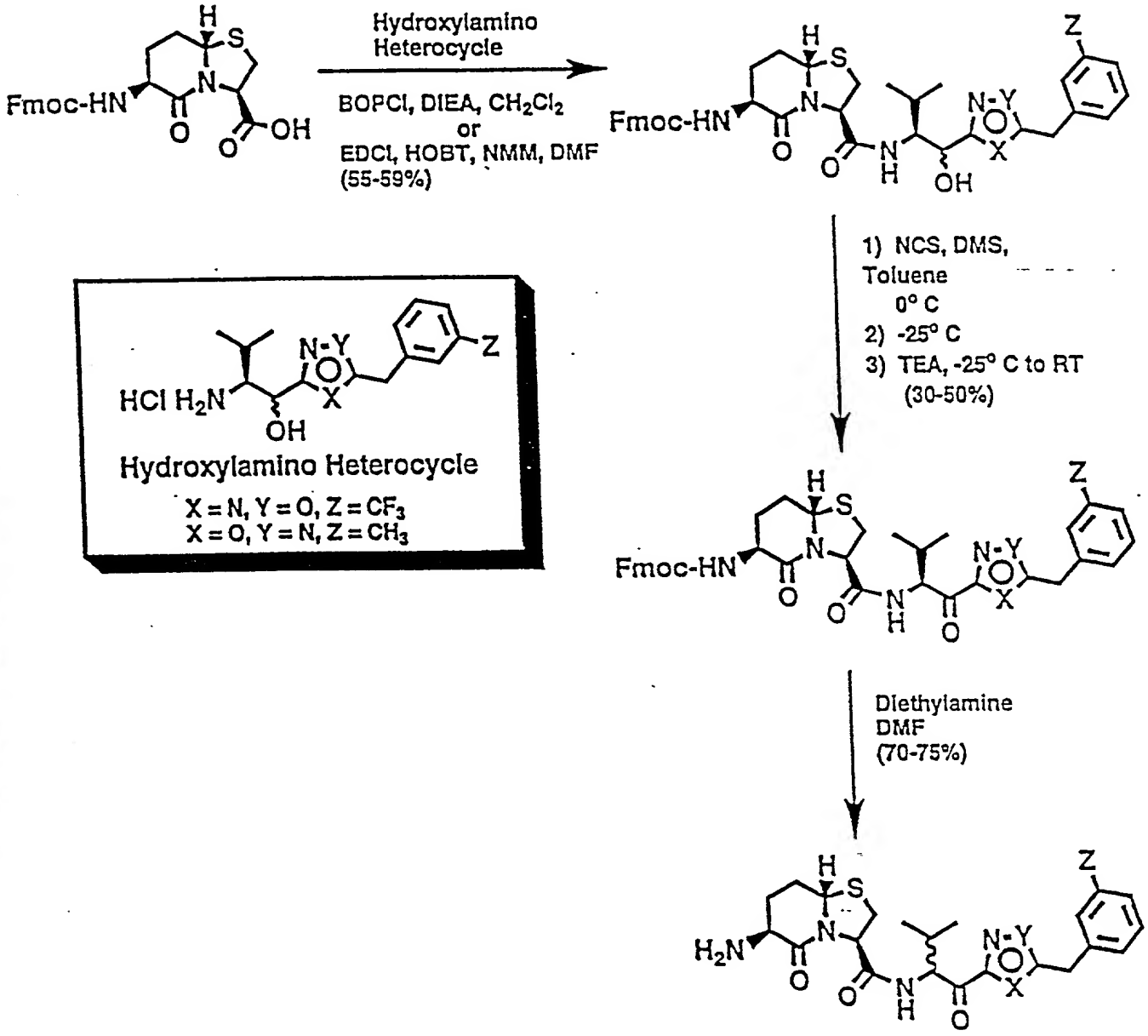


Figure 10

General Synthetic Scheme for P_2-P_3 Modified Inhibitors

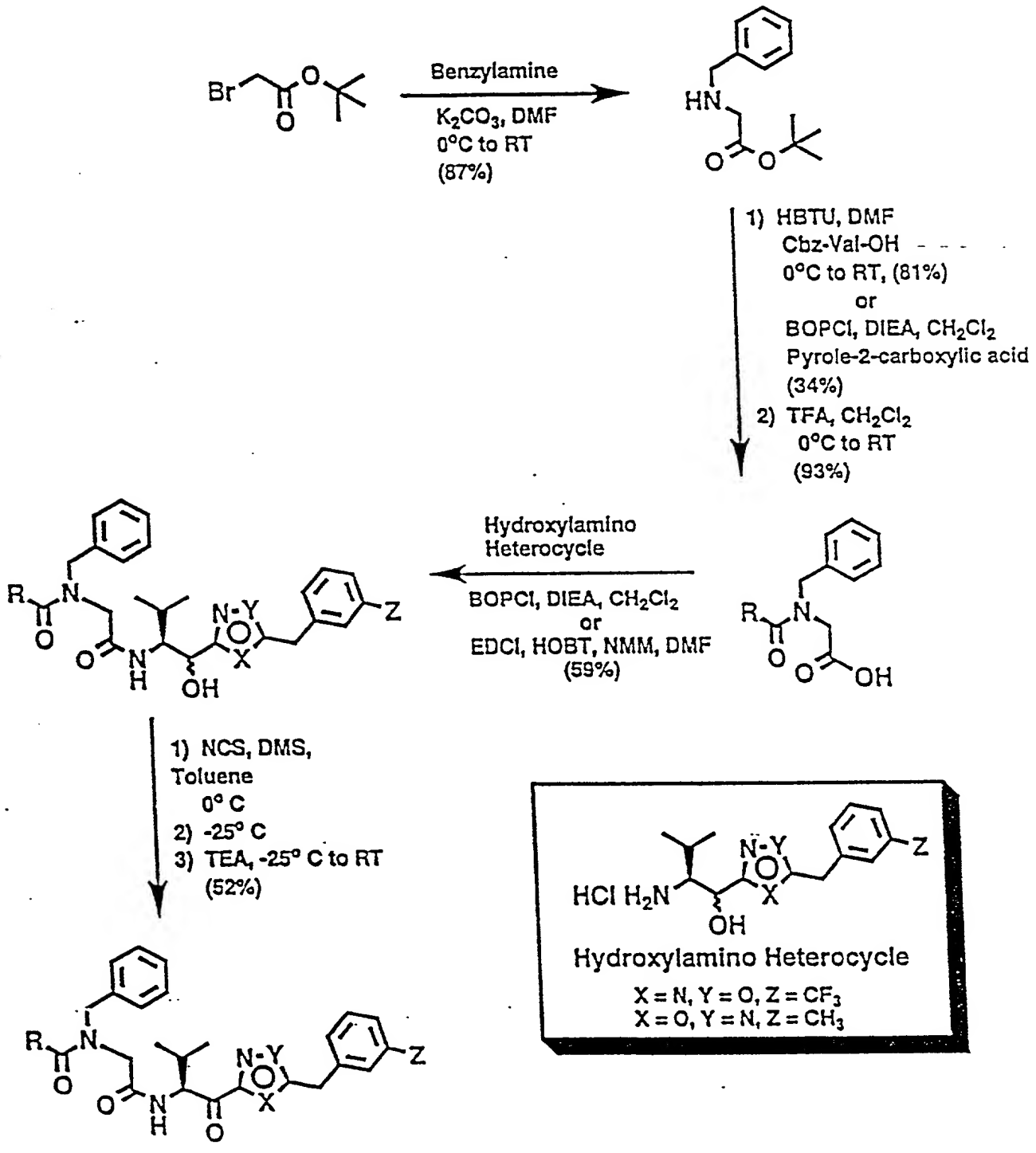


Figure 11

General Synthetic Scheme for P_2-P_3 Lactam Based Inhibitors

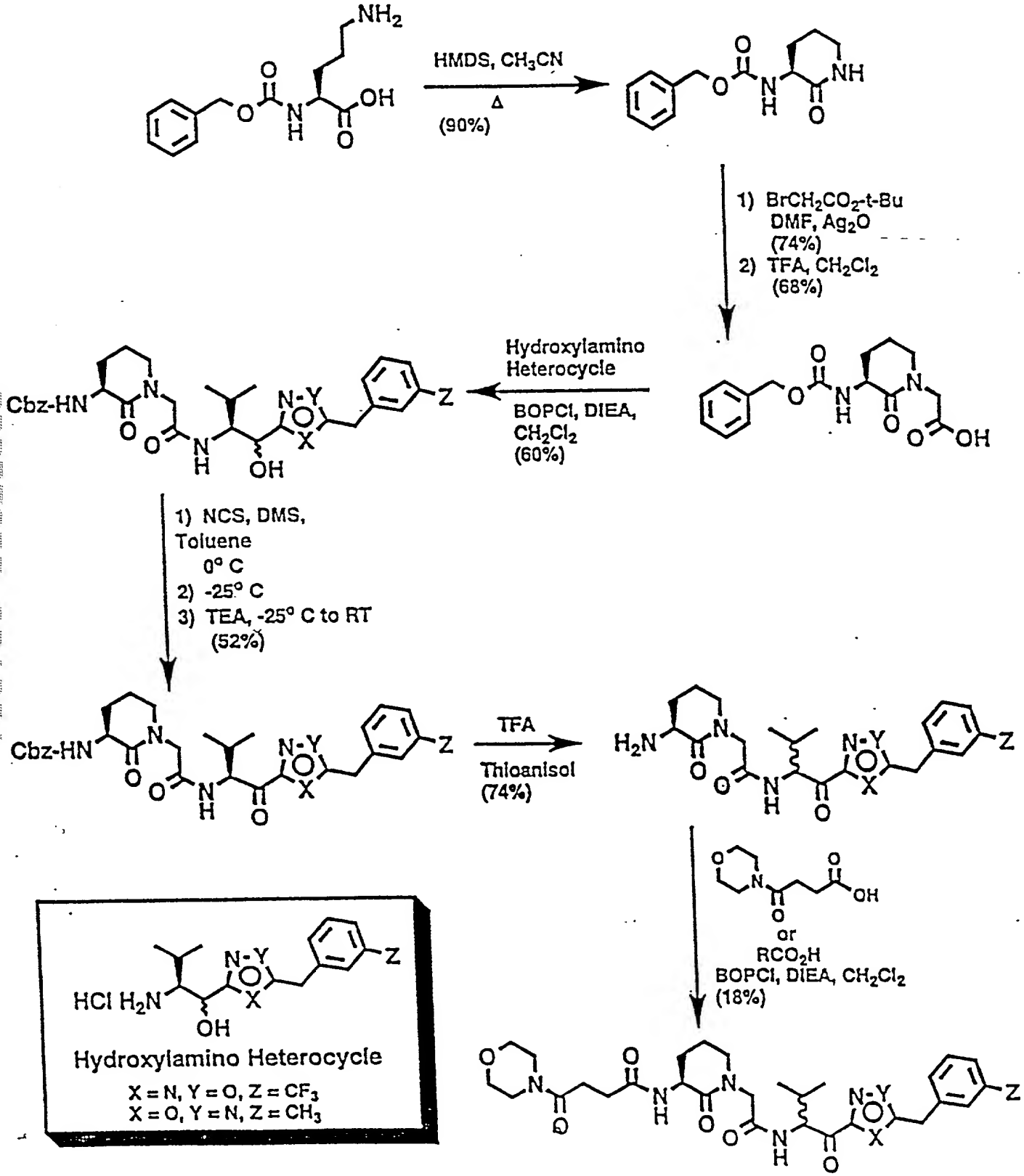


Figure 12

General Synthetic Scheme for P_2-P_3 Lactam Based Inhibitors

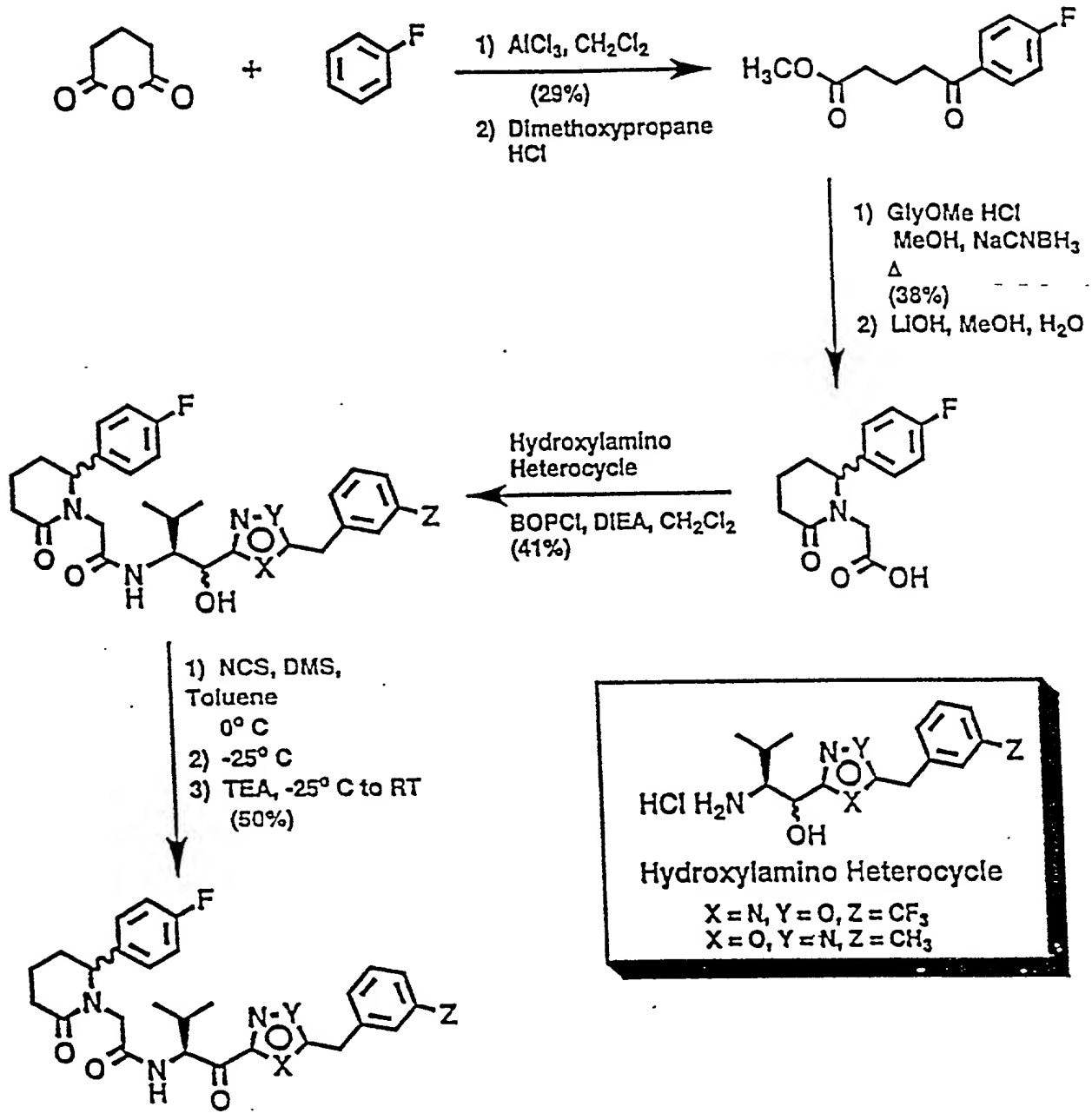


Figure 13

General Synthetic Scheme for Metathiazanone Based Inhibitors

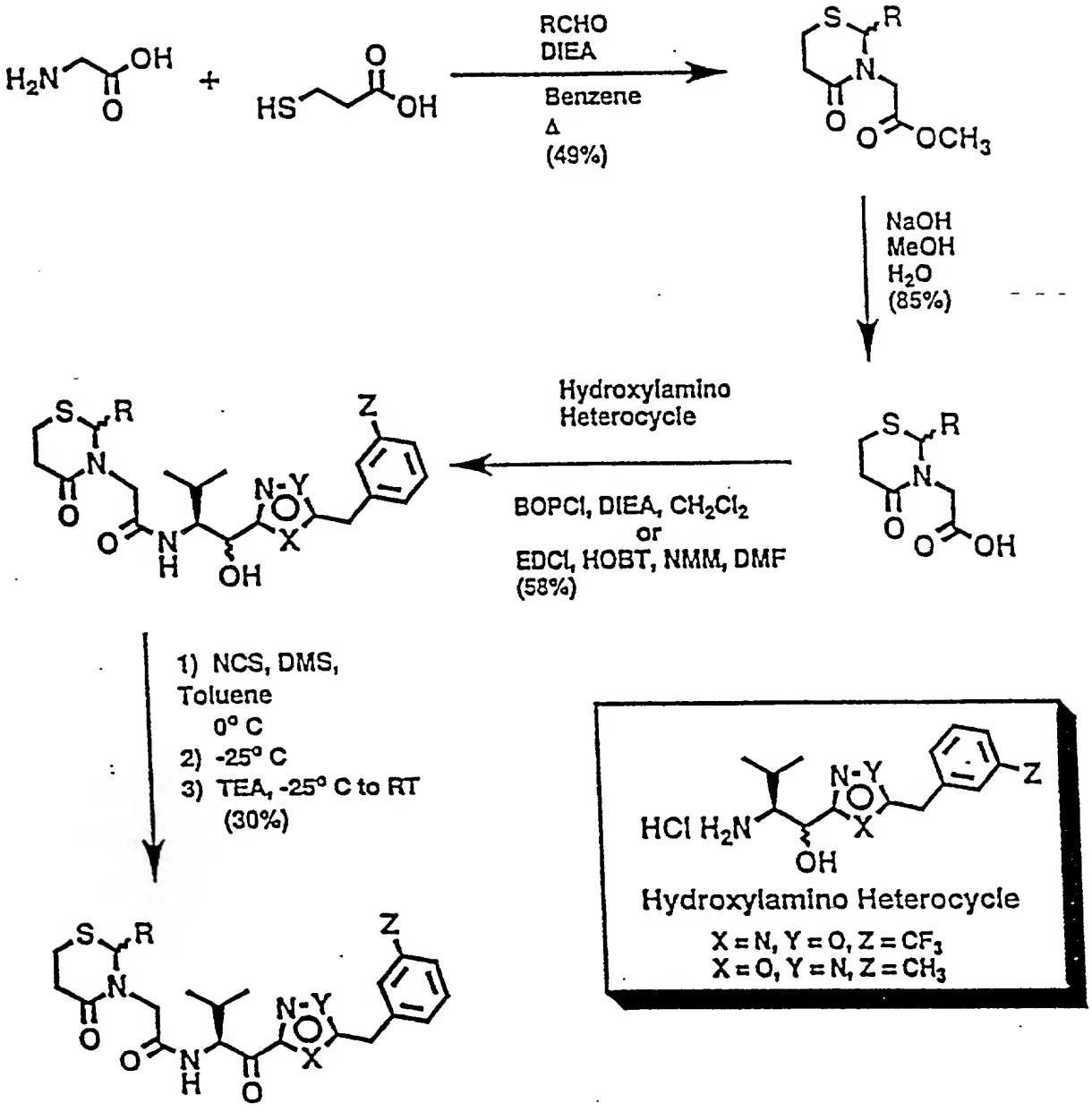


Figure 14

General Synthetic Scheme for Thiazolidinone Based Inhibitors

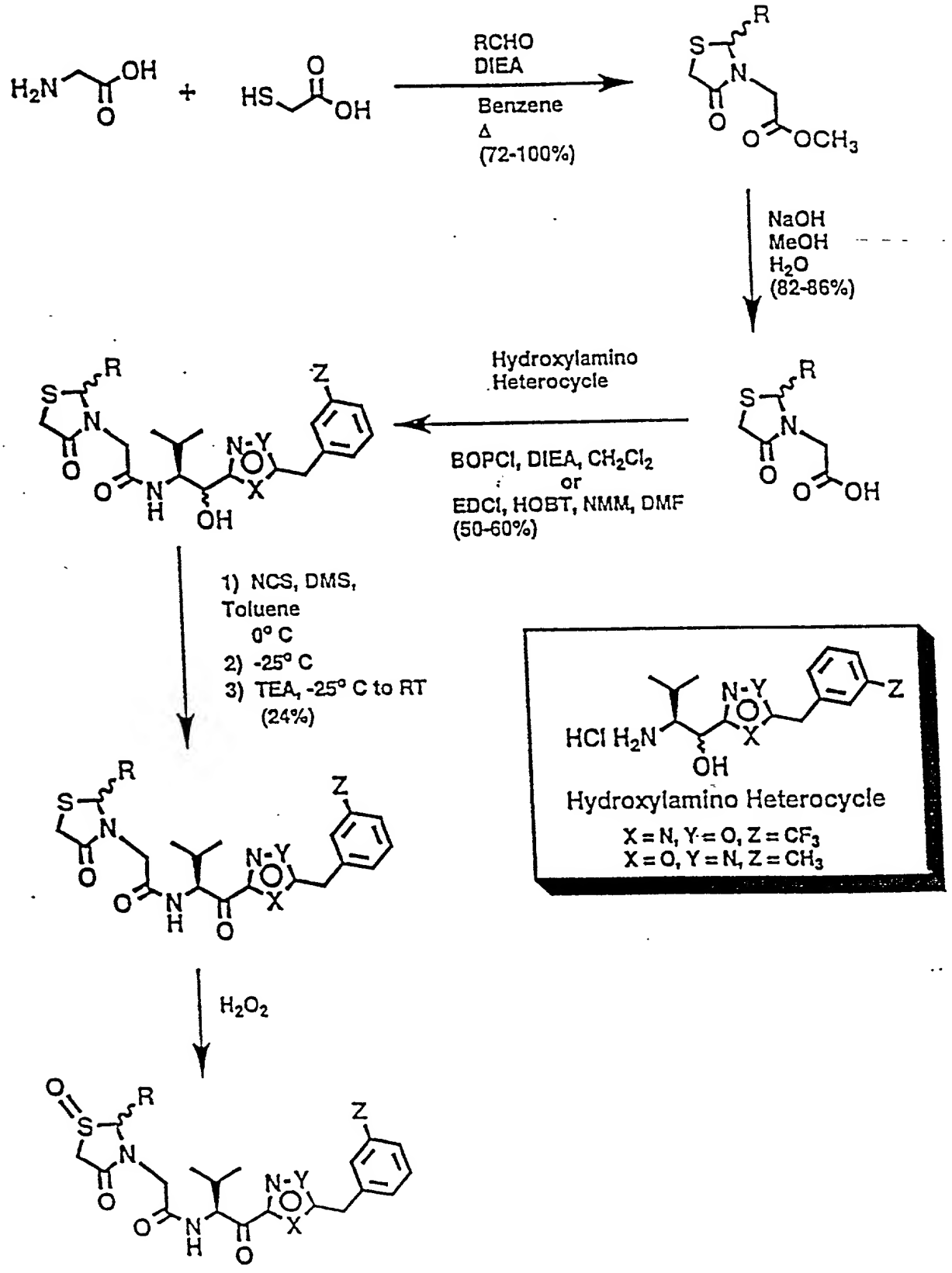


Figure 15

General Synthetic Scheme for Pyridazinedione Based Inhibitors

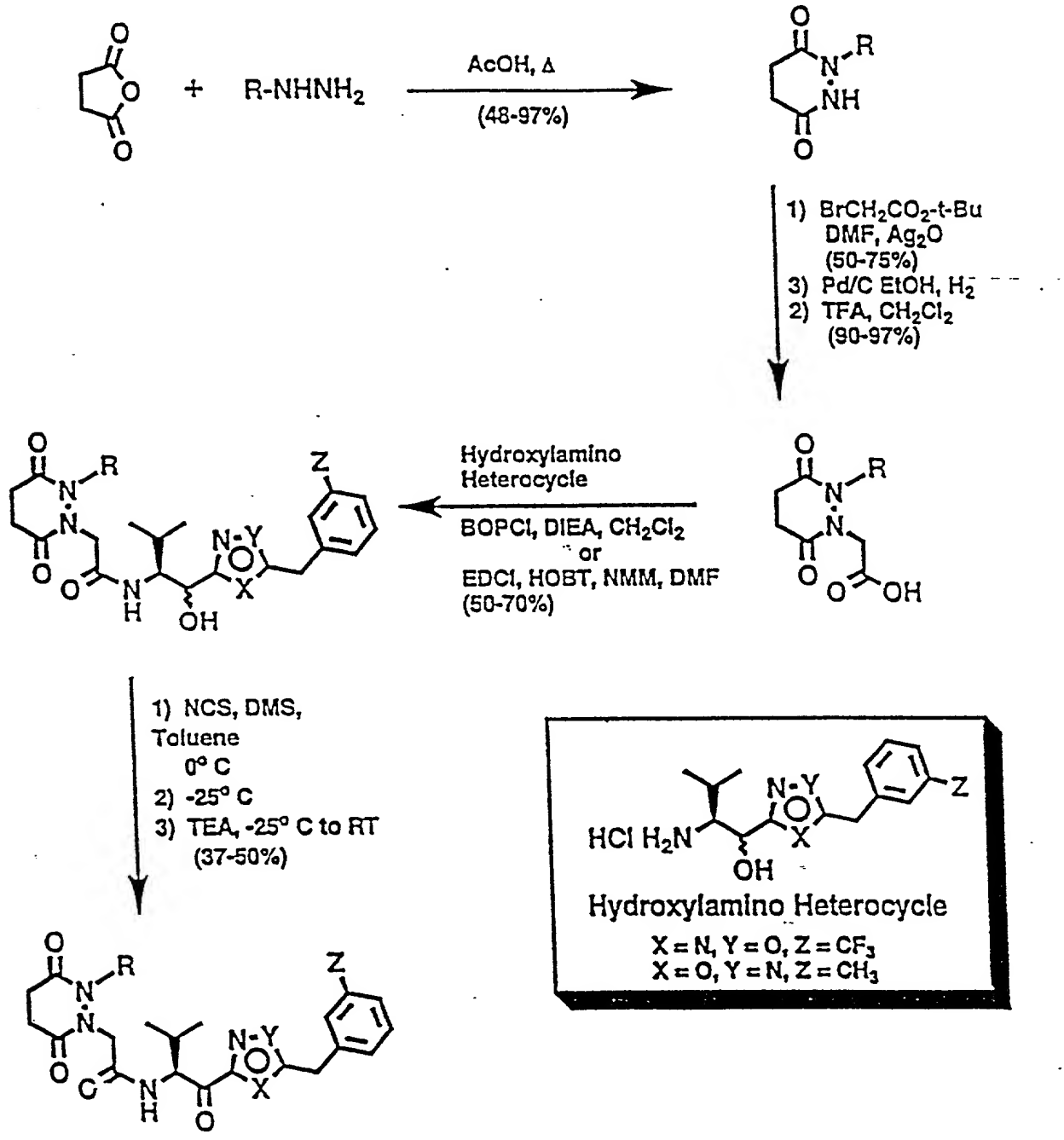


Figure 16

General Synthetic Scheme for Benzopyridazinedione Based Inhibitors

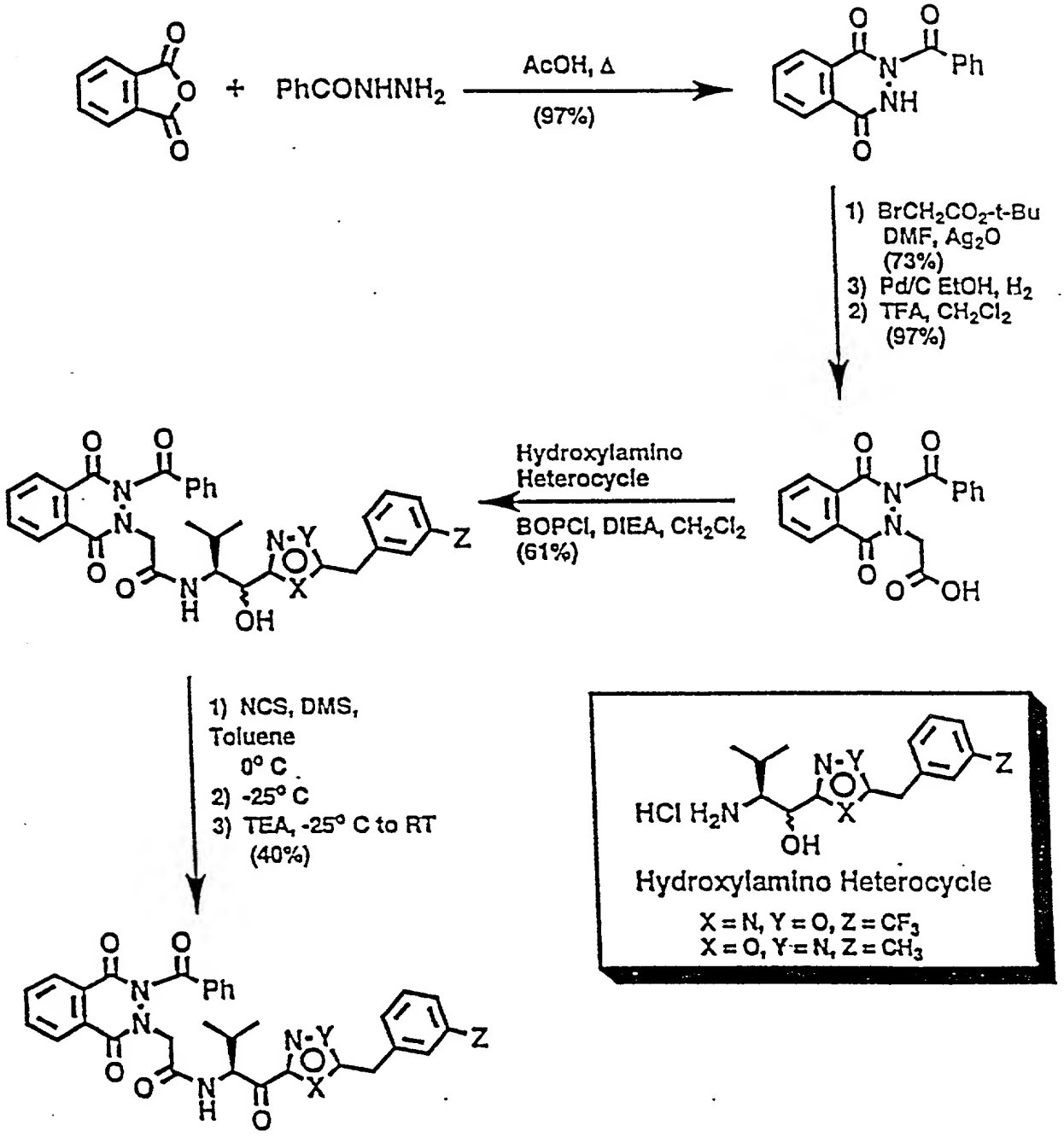


Figure 17

General Synthetic Scheme for Quinolone and N-Substituted Quinolone Based Inhibitors

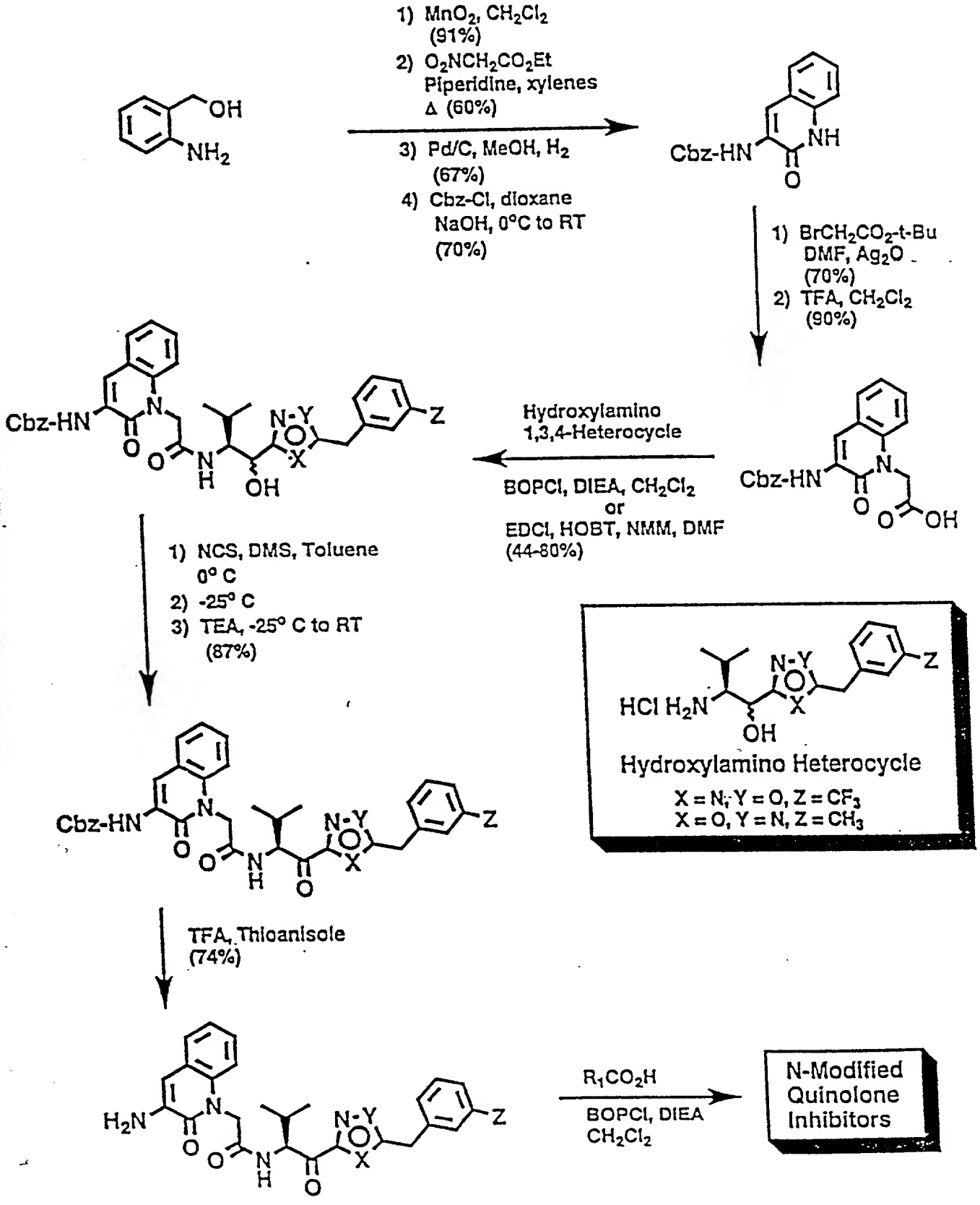


Figure 18

General Synthetic Scheme for 3,4-Dihydroquinolone Based Inhibitors

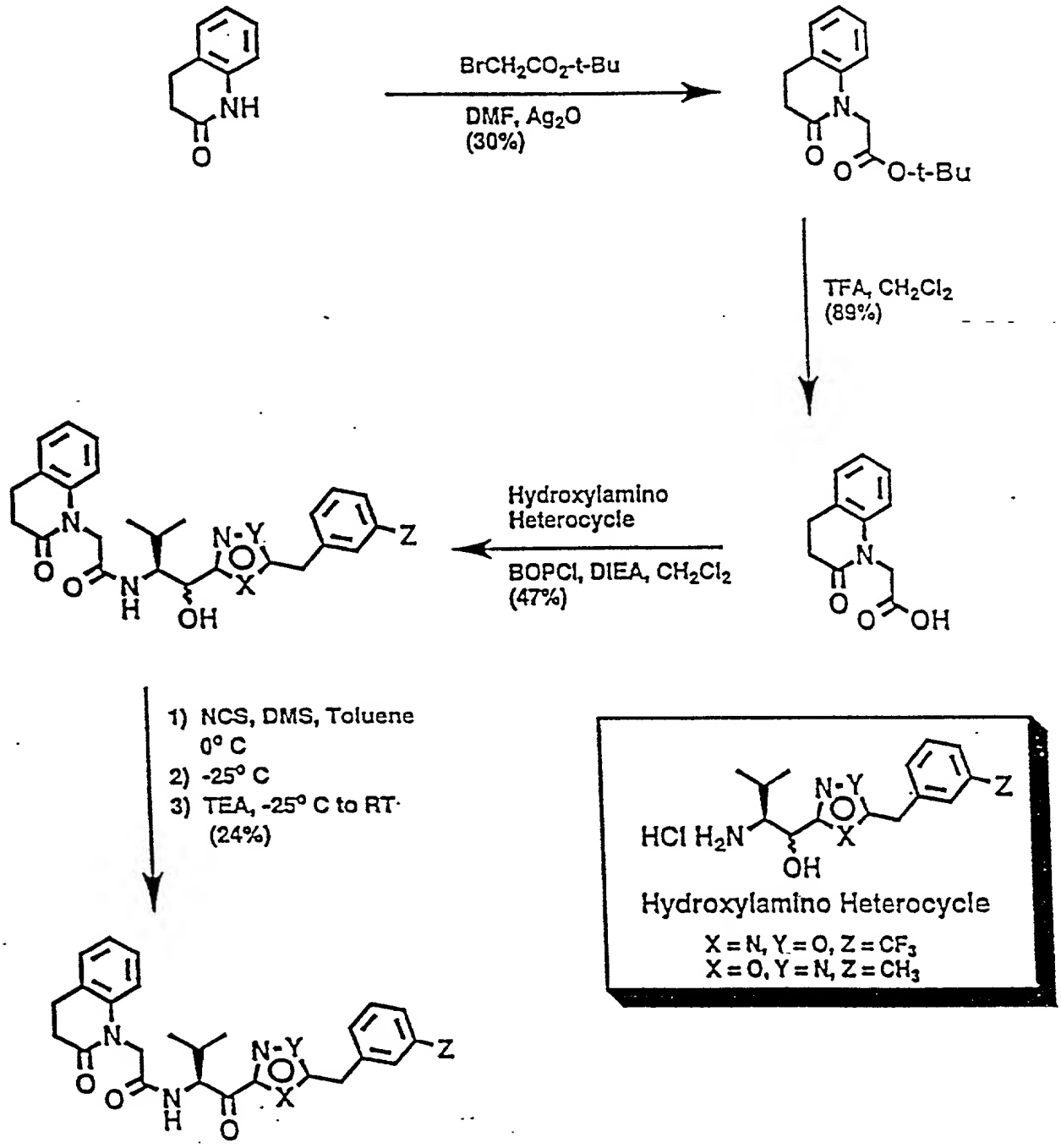


Figure 19

General Synthetic Scheme for Benzylidene Diketopiperazine Based Inhibitors

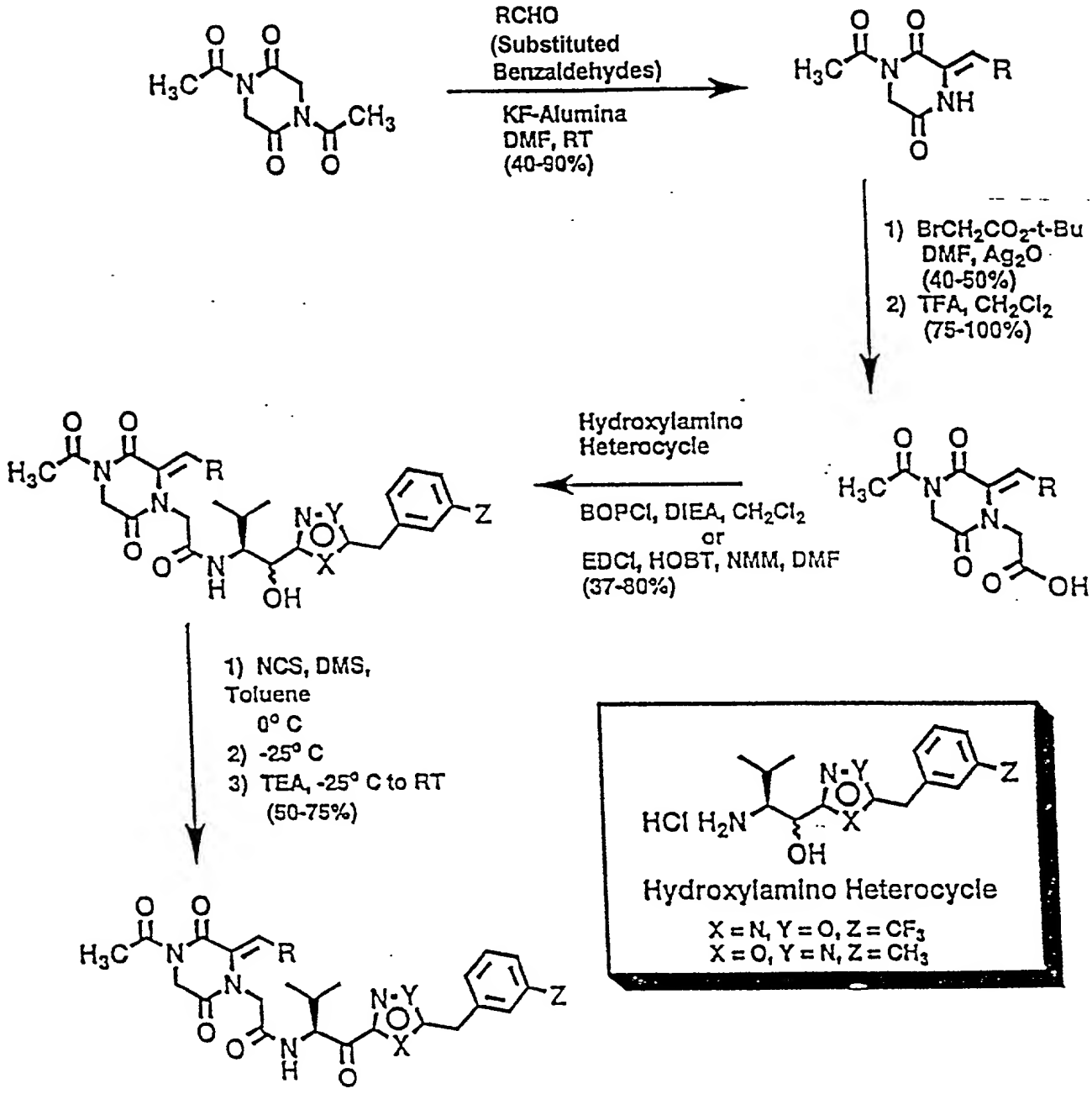


Figure 20

General Synthetic Scheme for Diketopiperazine Based Inhibitors

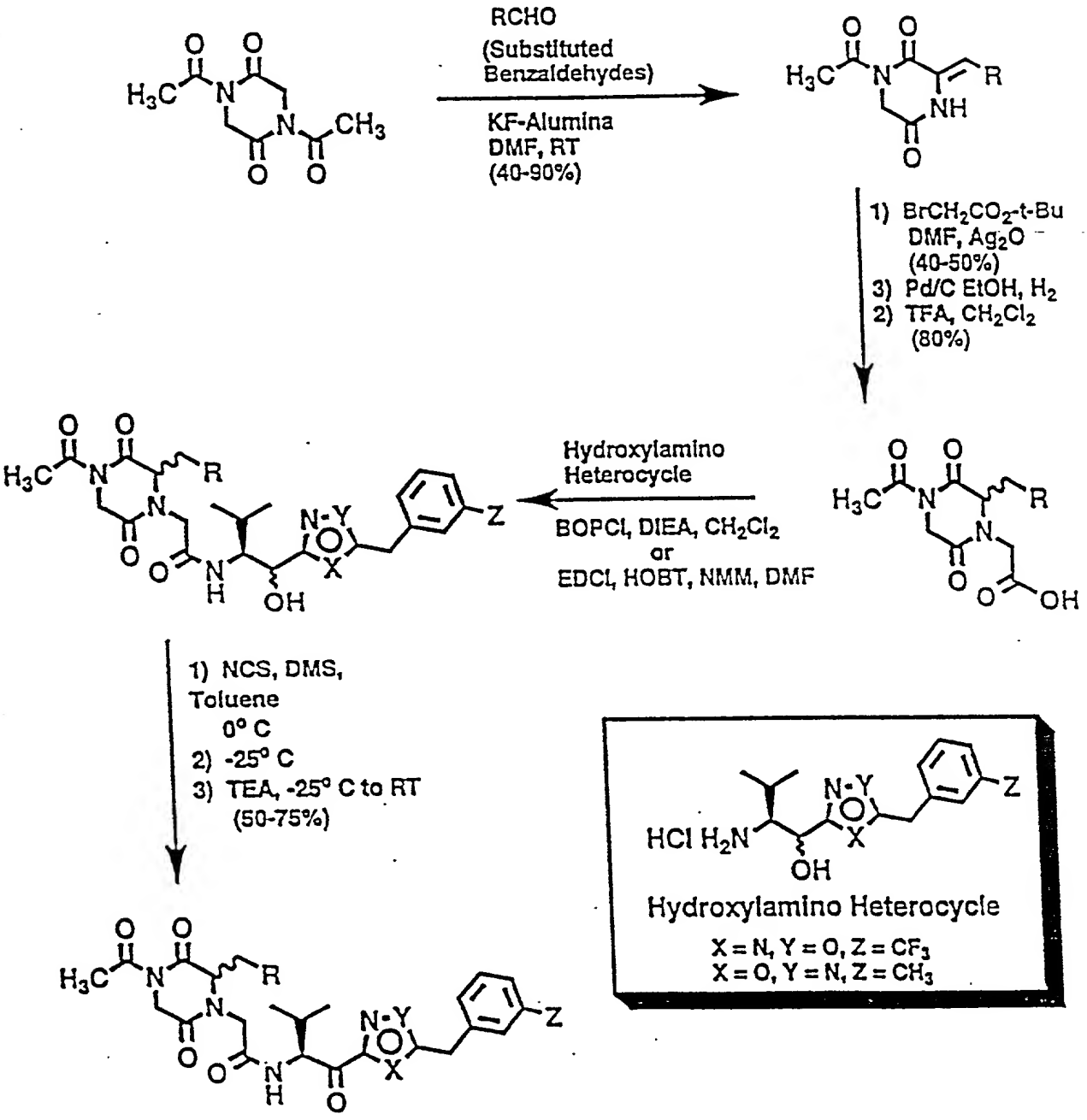


Figure 21

Synthetic Scheme for Hydantoin Based Inhibitors

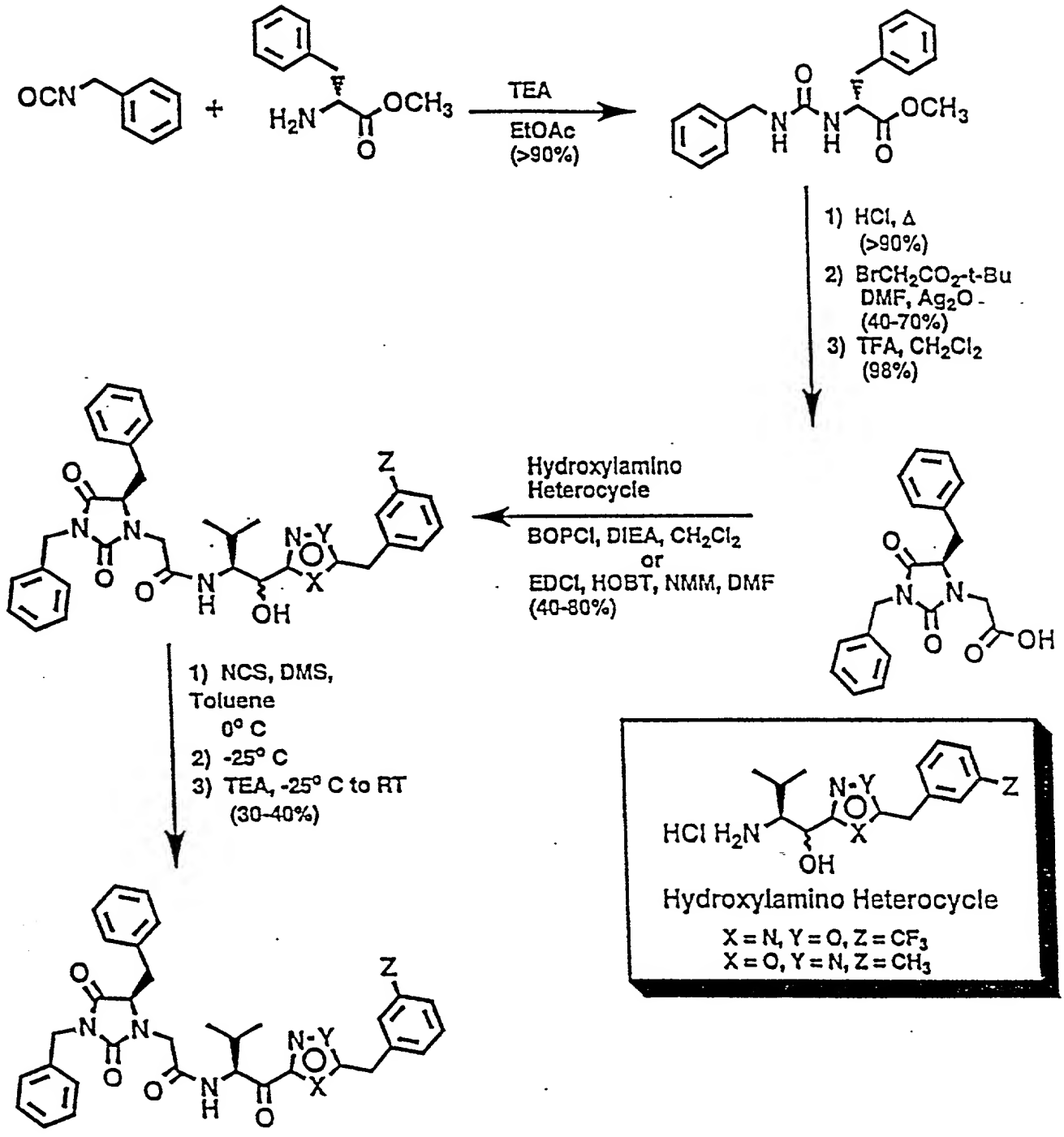


Figure 22

General Synthetic Scheme for Hydantoin Based Inhibitors

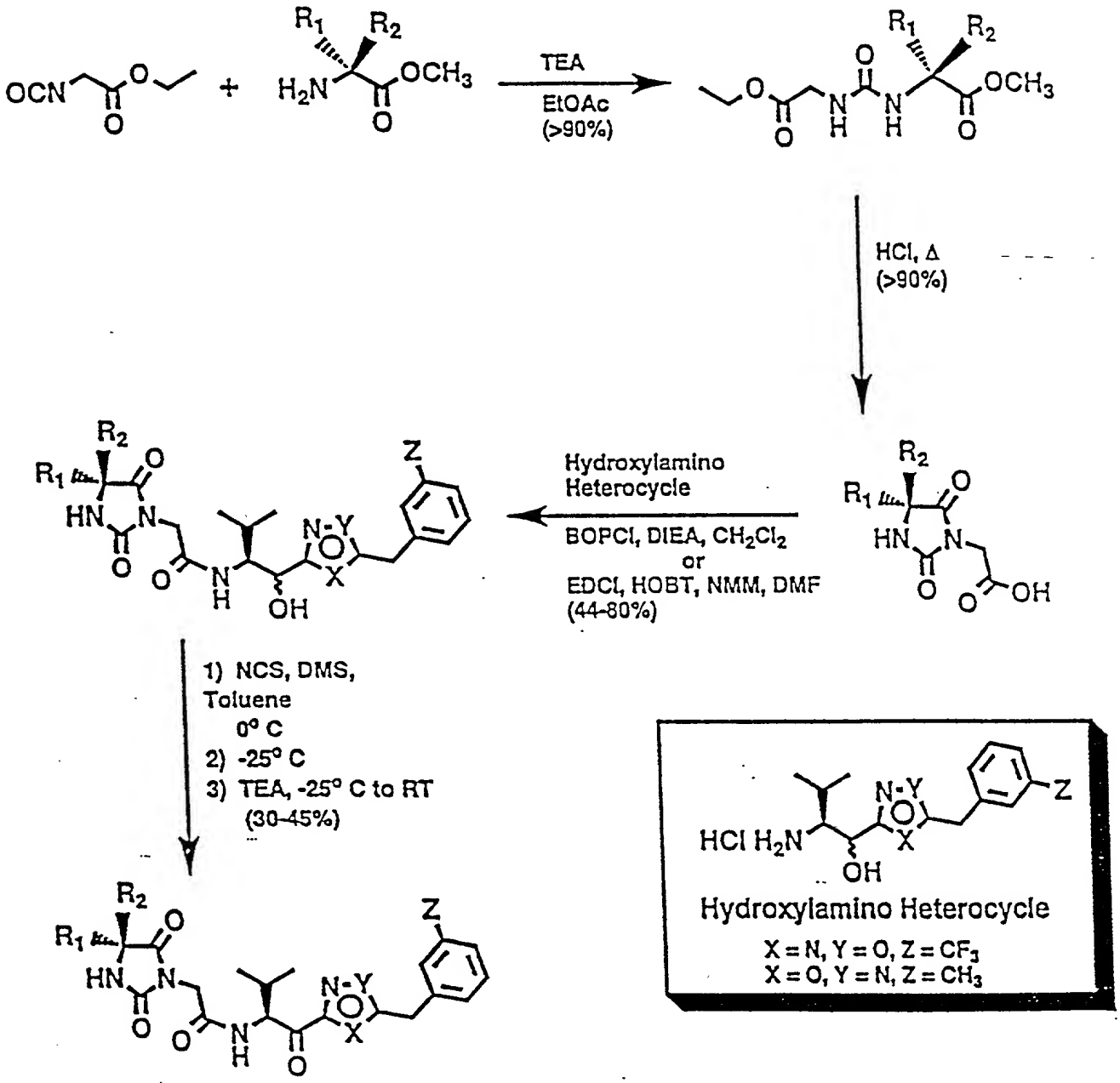
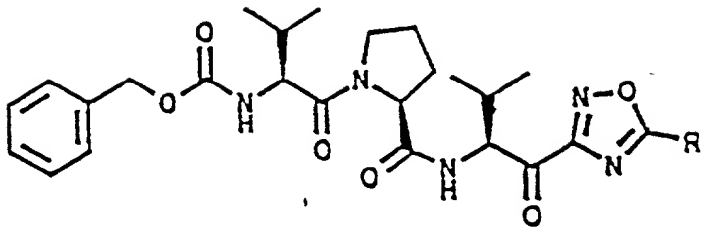


Figure 23



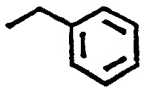
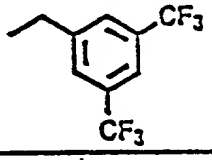
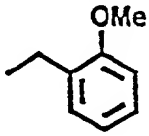
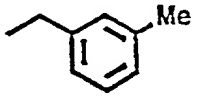
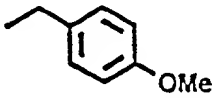
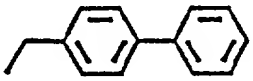
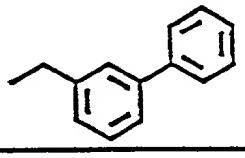
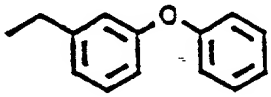
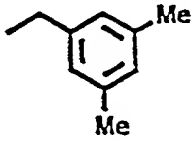
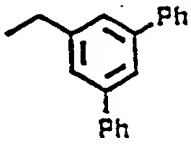
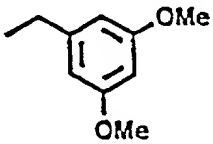
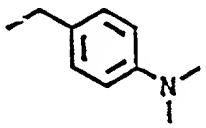
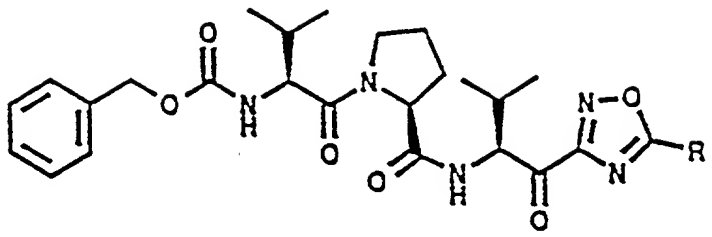
CE#	R	K_I (nM)	CE#	R	K_I (nM)
2039		2.0	2054		0.29
2042		2.5	2055		0.49
2045		1.0	2058		0.56
2048		0.36	2062		0.30
2049		0.5	2066		0.98
2052		0.37	2096		0.8
2053		0.41	2115		1.0

Figure 24



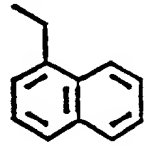
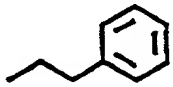
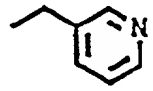
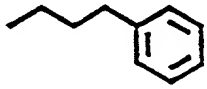
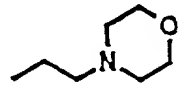
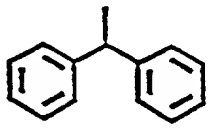
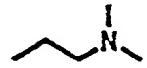
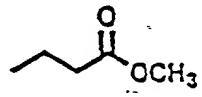
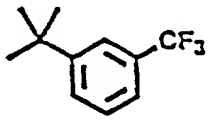
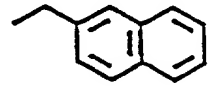
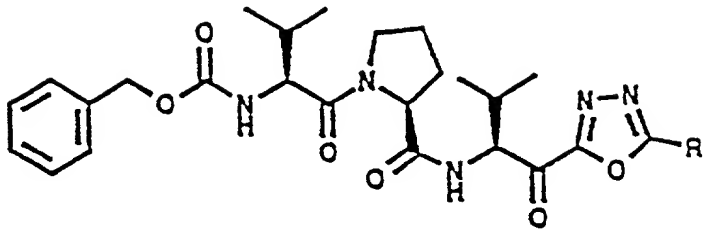
CE#	R	K_I (nM)	CE#	R	K_I (nM)
2046		9.9	2077		0.15
2047		3.8	2078		1.05
2050		1.84	2092		6.3
2057		0.38	2103		12.4
2069		4.4	2119		7.7
2073		0.24	2152		0.24
2076		1.46			

Figure 25



CE#	R	K_i (nM)
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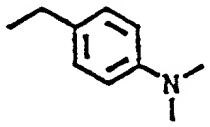
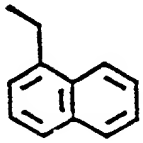
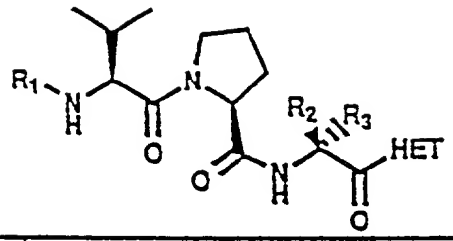
2074	$-CH_3$	0.99
2075		0.11
2100		0.069
2123		15.1
2124		0.033

Figure 26



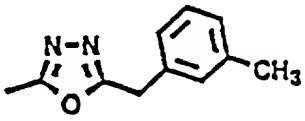
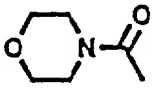
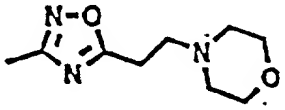
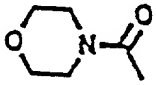
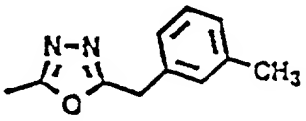
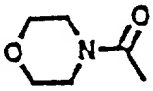
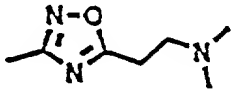
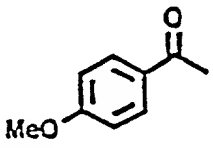
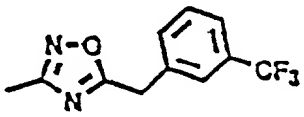
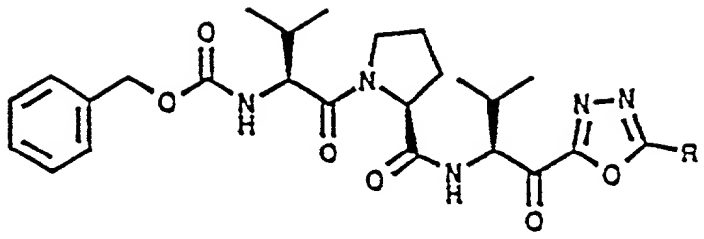
CE#	R_1	R_2	R_3	HET	K_i (nM)
2083	Cbz-	CH_3	CH_3		73.0
2098		*i*-Propyl	H		85.0
2104		*i*-Propyl	H		0.33
2109		*i*-Propyl	H		126
2110		*i*-Propyl	H		0.13

Figure 27



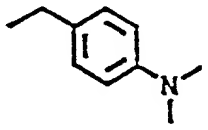
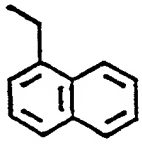
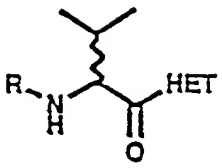
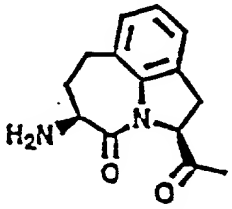
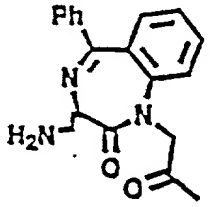
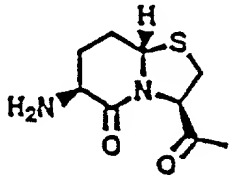
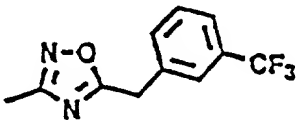
CE#	R	K_i (nM)
2072		0.025
2074	$-CH_3$	0.99
2075		0.11
2100		0.069
2123		15.1
2124		0.033

Figure 28

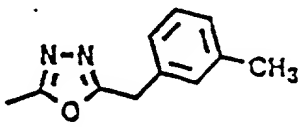


CE#	R	HET	K_I (nM)
2130		B	10.0
2132		A	24.0
2134		B	2.0
2135		A	17
2126		B	5.05
2127		A	33.9

Heterocycles:

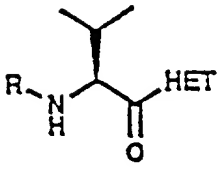


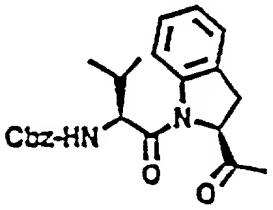
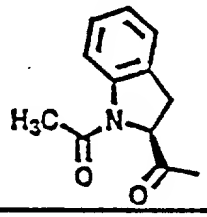
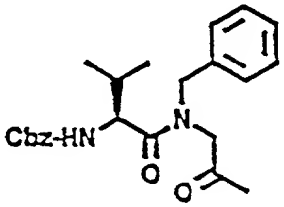
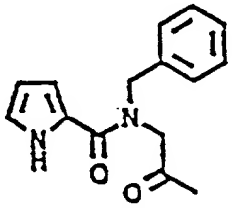
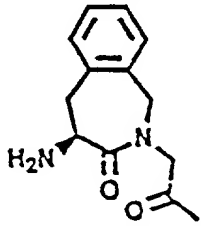
A



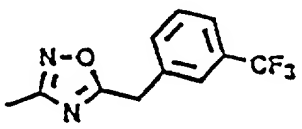
B

Figure 29

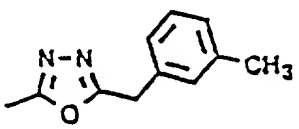


CE#	R	HET	K_I (nM)
2125		A	0.40
2145		B	0.038
2143		A	25.0
2056		A	0.98
2097		A	60.0
2156		A	512.0

Heterocycles:

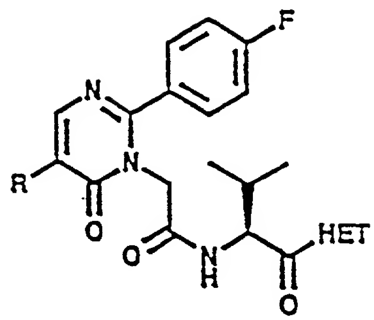


A



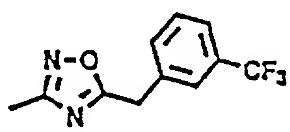
B

Figure 30

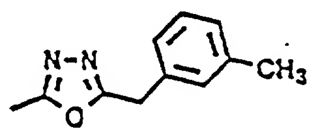


CE#	R	HET	K_I (nM)
2089	Cbz-NH-	A	1.5
2090	NH_2-	A	2.7
2095	Cbz-NH-	B	0.21
2101	NH_2-	B	0.64

Heterocycles:

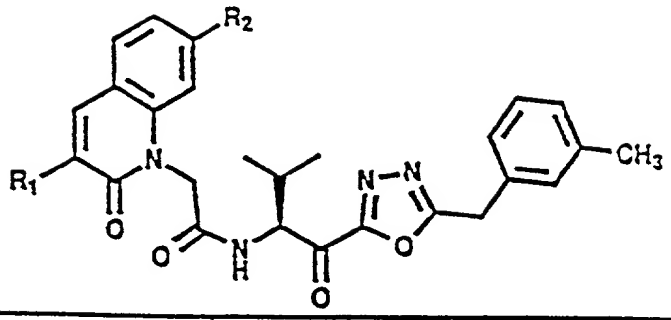


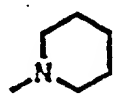
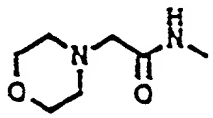
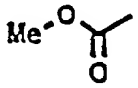
A

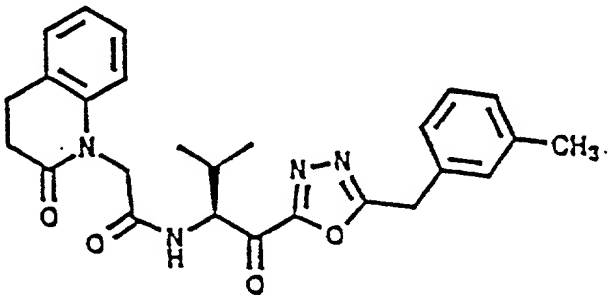


B

Figure 31

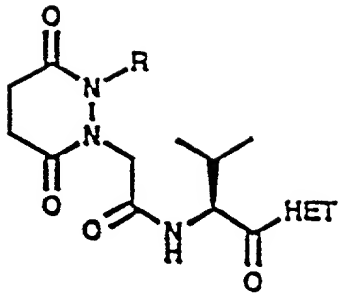


CE#	R_1	R_2	K_i (nM)
2107	Cbz-NH-		17.0
2108	Cbz-NH-	H	10.5
2113	H_2N-	H	38.8
2116		H	76.3
2117		F	587.0

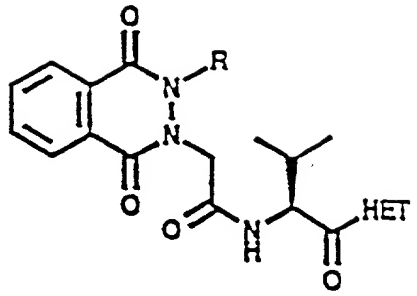


CE-2088 K_i = 66.0 nM

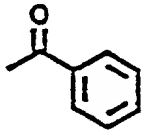
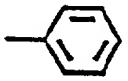
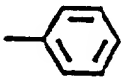
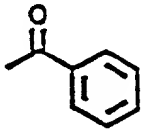
Figure 32



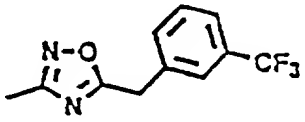
I



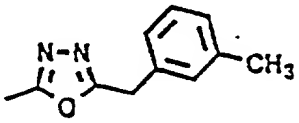
II

CE#	R	Structure	HET	K_i (nM)
2138		I	B	294.0
2147		I	B	1590
2148		I	A	>6000
2140		II	B	204.4

Heterocycles:

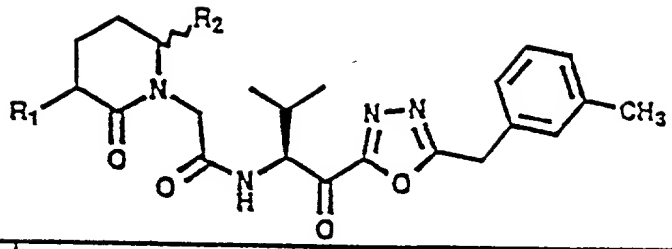


A



B

Figure 33



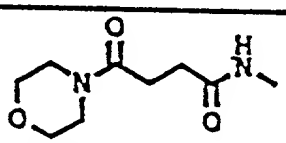
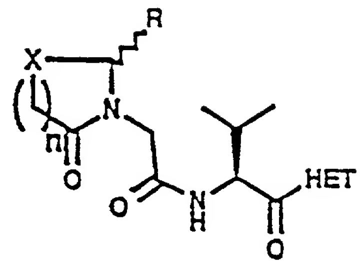
CE#	R_1	R_2	K_i (nM)
2079	Cbz-NH-	H	35.5
2080	H_2N-	H	62.0
2087	H		19.8
2091		H	270.0

Figure 34



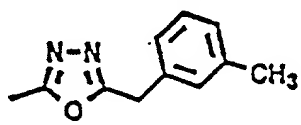
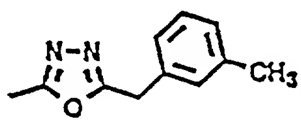
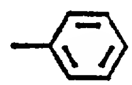
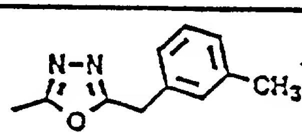
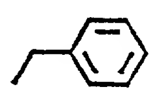
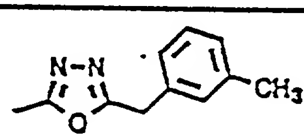
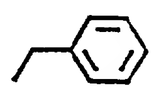
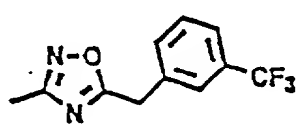
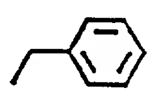
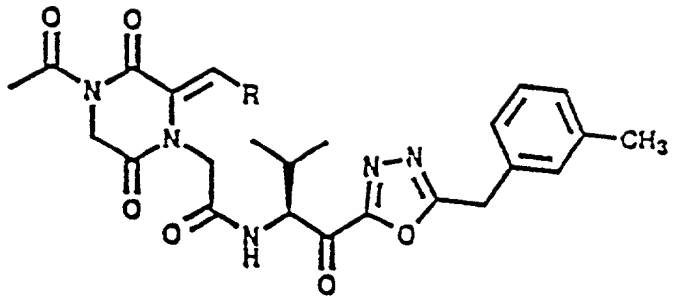
CE#	n	X	HET	R	K_i (nM)
2118	2	S			13.2
2121	1	S			28.0
2122	1	S			62.7
2136	1	SO			104.0
2137	1	SO			557.0

Figure 35



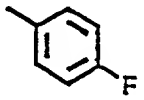
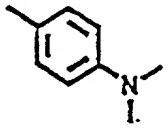
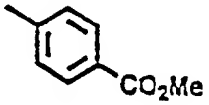
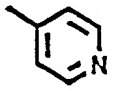
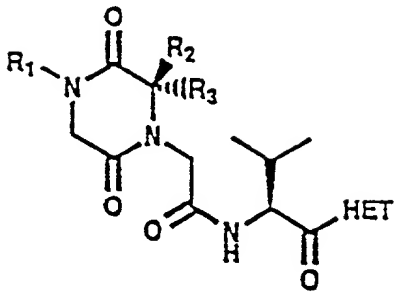
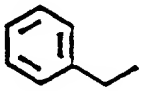
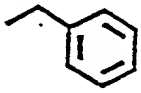
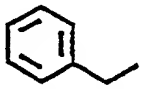
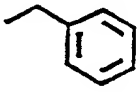
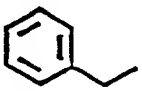
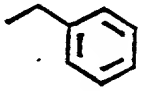
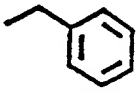
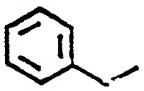
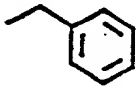
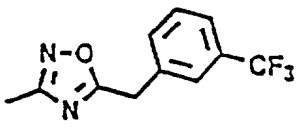
CE#	R	K_i (nM)
2099		1.9
2105		0.72
2111		20.1
2112		1.17
2114		25.1

Figure 36

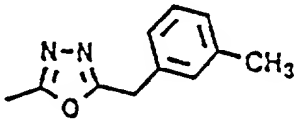


CE#	R_1	R_2	R_3	HET	K_i (nM)
2084	CH_3			A	133.0
2106	CH_3			B	40.7
2120	CH_3CO-			B	50.9
2128		—H		B	64.0
2129		—H		A	300.3
2133		—H		C	33200
2139	H—			B	41.0
2144			—H	B	9.3
2146			—H	A	67.3

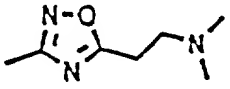
Heterocycles:



A

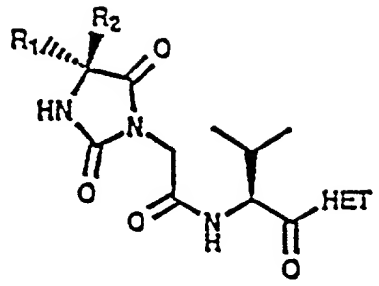


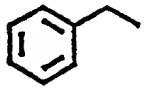
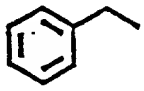
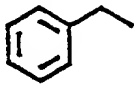
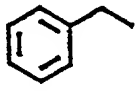
B



C

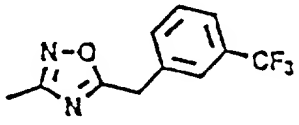
Figure 37



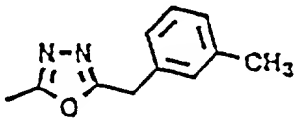
CE#	R_1	R_2	HET	K_i (nM)
2141		H	A	64.0
2142		H	B	8.7
2149**		H	B	0.28
2154	H		B	10.0
2155	H		A	57.0

** Stereochemistry not definitive

Heterocycles:

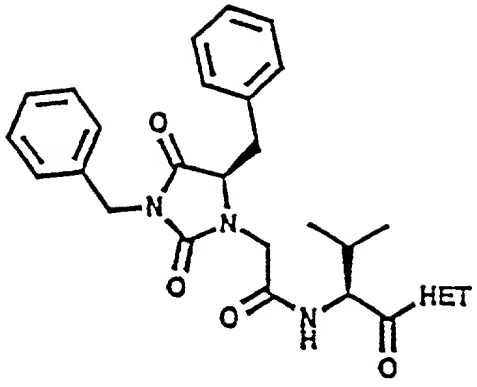


A



B

Figure 38



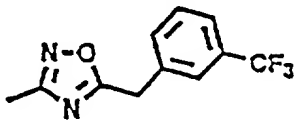
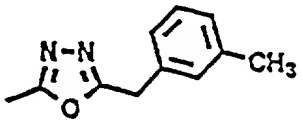
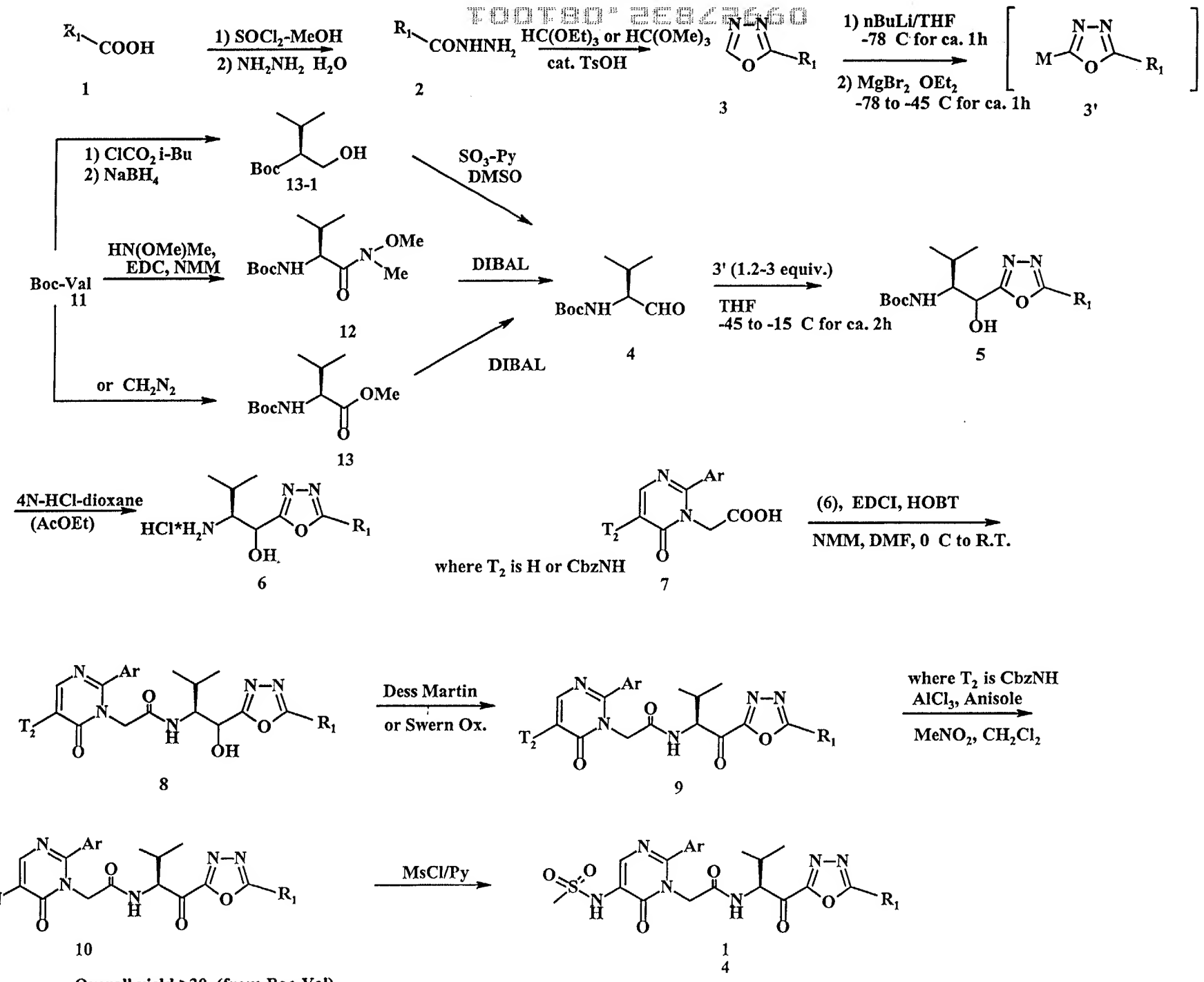
CE#	HET	K_I (nM)
2150		>1000
2151		60

Fig - Synthesis of ONO-PO series compounds



Overall yield >30 (from Boc-Val)